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Unveiling the Hepatoprotective and Ameliorative Potential of Natural Products in Paracetamol Overdose

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Abstract

Paracetamol (Acetaminophen; N-acetyl-P- aminophenol) is a broadly used analgesic and antipyretic prescription that can have fatal side effects when used in high dosages. Conventional treatment options for paracetamol overdose are limited and often ineffective, highlighting the need for alternative therapies. In recent years, there has been a growing interest in exploring natural remedies as potential alleviating interventions for paracetamol overdose. This comprehensive review explores the evidence-based natural therapies that have been studied for their effectiveness in reducing paracetamol toxicity. The review examines the mechanisms of action and safety profiles of these natural therapies, as well as their potential limitations and future research directions. The natural remedies discussed in this review include N-acetylcysteine, palm date, milk thistle, curcumin, ginger, and several others. Overall, this review highlights the potential of certain traditional hepatoprotective plants as effective and safe protective options against paracetamol overdose and emphasizes the need for further research to establish their clinical efficacy and safety.

Keywords: Paracetamol, toxicity, N-acetyl cysteine, natural therapy

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Introduction

Paracetamol (Acetaminophen; N-acetyl-P-aminophenol) is a generally used analgesic and antipyretic prescription that has been accessible over the counter for decades [1]. It is frequently used to relieve headaches and mild aches and reduce fever, menstrual cramps, and back pain [2]. However, overuse or misuse of paracetamol can lead to liver damage and other serious health complications.

Overdose of paracetamol, which refers to taking more than three grams per day, is a frequent cause of acute liver failure, gastric ulcers, and impaired reproductive function [1, 3, 4]. If left untreated, it can lead to significant morbidity and mortality. The toxicity of paracetamol occurs through the production of N-acetyl-p-benzoquinone imine (NAPQI) reactive metabolites that can trigger oxidative stress, mitochondrial dysfunction, and inflammation, leading to hepatic damage [5]. While N-acetylcysteine (NAC) is the typical treatment for paracetamol overdose, its effectiveness is restricted in some cases, mainly in patients with late or pre-existing liver disease [6].

More and more attention is being given to the investigation of natural products as potential protectants against paracetamol toxicity. Natural products such as herbal extracts and phytochemicals have been found to have antioxidant, anti-inflammatory, and hepatoprotective characteristics, which could potentially alleviate the harmful effects of an overdose of paracetamol. In this review, we will provide a comprehensive summary of the mechanisms underlying paracetamol toxicity, its clinical manifestations, and conventional treatment options, as well as discuss the potential hepatoprotective effects of some traditional plants against paracetamol toxicity.

Mechanisms of paracetamol toxicity

Paracetamol is rapidly absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism in the liver [7]. At therapeutic doses, about 90% of paracetamol breaks down by conjugation with glucuronic acid and sulfate, leading to the formation of non-toxic metabolites that are eliminated in the urine [1, 8]. However, a minor pathway (10% of paracetamol) involving oxidation by cytochrome P450 enzymes (particularly CYP2E1) leads to the formation of NAPQI, a highly reactive metabolite that can deplete cellular glutathione (GSH) and covalently binds to mitochondria, triggering reactive oxygen species (ROS) generation and reactive nitrogen species (RNS) [5, 9, 10]. The subsequent mitochondrial oxidant/nitrosative stress is further amplified by c-Jun N-terminal kinase (JNK) and triggers permanent mitochondrial permeability transition pore opening causing mitochondrial damage that leads to nuclear DNA damage, necrotic cell death, and inflammation [11]. In summary, the depletion of glutathione, oxidative stress, and damage to mitochondria are

the main mechanisms behind paracetamol toxicity, as depicted in Figure 1.

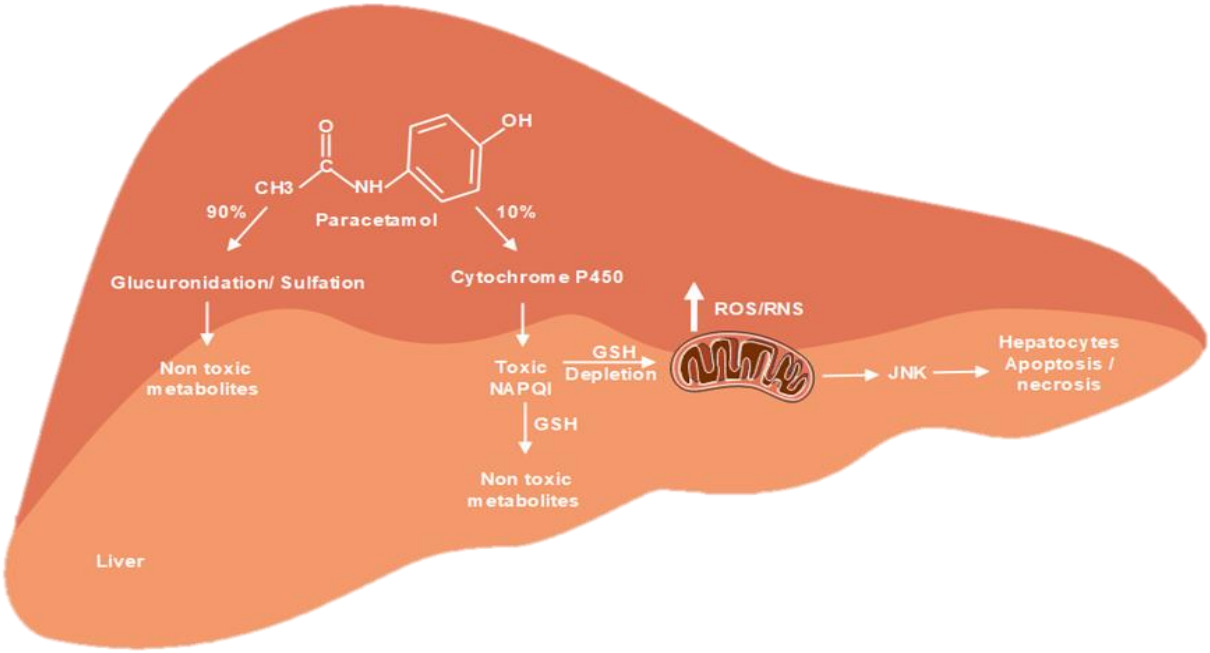

Figure 1: The diagram illustrates the process of paracetamol metabolism, which involves two main pathways: glucuronidation and sulfation. These pathways result in the formation of harmless metabolites that are eliminated from the body through the kidneys. In addition, paracetamol can also undergo minor metabolism through CYP2E1 enzymes, resulting in the production of a toxic metabolite called N-acetyl-p-benzoquinone imine (NAPQI). To prevent harm, NAPQI is quickly detoxified by binding to GSH's sulfhydryl group, forming cysteine and mercapturic acid conjugates that are excreted in the urine. However, when the liver is deficient in GSH, NAPQI accumulates and leads to the formation of ROS/RNS, which trigger hepatocyte cell death.

Clinical manifestations of paracetamol toxicity

Paracetamol toxicity can occur following acute overdose or chronic ingestion of supra-therapeutic doses. In acute overdose, symptoms typically occur within 24 hours and include nausea, vomiting, abdominal pain, and diaphoresis [7]. As the toxicity progresses, jaundice, coagulopathy, encephalopathy, and multi-organ failure may develop [7].

Chronic ingestion of supra-therapeutic doses can cause a subacute form of liver injury that may present with nonspecific symptoms, such as fatigue and malaise, and can progress to cirrhosis, end-stage liver disease, and kidney failure as well [12]. Laboratory findings that support the diagnosis of paracetamol toxicity include elevated transaminases (AST and ALT), bilirubin, prothrombin time, and declining bicarbonate [7].

Conventional treatment of paracetamol toxicity

Paracetamol poisoning can be treated with N-acetyl cysteine (NAC), which serves as an antidote [13]. NAC acts as a precursor to cysteine, which in turn is a precursor to glutathione. By increasing the detoxification of NAPQI, either through direct conjugation with GSH or by enhancing GSH synthesis, NAC can counter the toxic effects of paracetamol by preventing the accumulation of harmful metabolites [14]. This process allows for the replenishment of hepatic glutathione stores and the scavenging of reactive oxygen species [7].

NAC can be administered orally or intravenously, with the intravenous route being preferred in patients with severe toxicity or compromised oral intake [12]. For effective treatment, NAC should be given within 8 hours of the ingestion of the overdose. However, Adio, Yinusa [7] suggest that it can still be useful when given up to 24 hours after ingestion. Despite being an effective antidote for paracetamol toxicity, NAC has some unpleasant side effects, such as nausea and vomiting [15].

Natural products with protective activity and their role in alleviating paracetamol toxicity

Herbal medicine is considered a preferable and safer alternative to conventional therapies due to its accessibility, cost-effectiveness, minimal side effects, and natural healing properties [16]. Natural products have been extensively investigated for their potential to prevent paracetamol-induced toxicity (Figure.2). The primary clinical treatment for paracetamol overdose involves administering NAC, which acts as a potent reactive oxygen species scavenger and suppresses oxidative stress [17]. Therefore, numerous plant-derived compounds have been assessed for their antioxidant activities and protective effects against paracetamol toxicity, and some of these plants and their potential benefits are mentioned below.

Figure 2: Plants with antioxidant and anti-inflammatory activities against paracetamol toxicity.

Traditional hepatoprotective plants and their role in alleviating paracetamol toxicity

Aloe vera (*Aloe barbadensis*)

Aloe barbadensis is a member of the Liliaceae family that thrives in hot and arid areas around the world [18]. Aloe vera is traditionally used in herbal medicine in Egypt, China, and India to treat microbial and viral infections and skin disorders [19]. It contains polyphenols, flavonoids, vitamin C, zinc, and selenium that possess anti-oxidant, anti-inflammatory, hypoglycemic, hypolipidemic, and hepatoprotective properties [2]. Studies have shown that aloe vera gel can reduce the severity of paracetamol-induced liver damage by enhancing the antioxidant level and preventing lipoperoxidation to counteract the oxidative stress environment [2, 3]. The animal dosage used in studies ranges from 400-500 mg/kg/day.

Basil or Rehan (*Ocimum basilicum*)

Basil is an annual herb in the Lamiaceae family that is widely cultivated throughout the globe [20]. Basil contains a variety of phytochemical components,

including flavonoids, phenolic acids, rosmarinic acid, aromatic compounds, and essential oils such as eugenol, chavicol, linalool, and a-terpineol [21]. These components showed antioxidant, anti-aging, anticancer, antiviral, and antimicrobial properties, as well as possible anti-stress, immunomodulatory, anti-inflammatory, antiapoptotic, and cell regeneration effects [20]. Studies have reported basil's protective effect against paracetamol through its antioxidant activity, radical scavenging activity, and suppression of lipid peroxidation [20-22]. The animal dosage of basil used in studies ranges from 200-600mg/kg/day.

Black mulberry (*Morus nigra*)

Black mulberry is a member of the Moraceae family's genus Morus [23]. Mulberry leaves are commonly used in traditional remedies for several health disorders, including urinary incontinence, respiratory disorders, diabetes, high blood pressure, cancer, and liver diseases [24]. They contain several compounds, including alkaloids, flavonoids, and steroids, and have been found to possess various beneficial activities such as antidiabetic, anti-atherosclerosis, anti-obesity, anti-aging, anti-inflammatory, antibacterial, antimicrobial, and neuroprotective activities [1, 24, 25]. Studies have also demonstrated its potential protective effects against paracetamol toxicity through its antioxidant activity, stimulation of glutathione transferases, and down-regulation of the p53 protein [1, 24]. The animal dosage used in studies ranges from 150 to 500 mg/kg/day.

Black seed (*Nigella sativa*)

Black seed is an annual herbaceous plant belonging to the Ranunculaceae family that grows in countries bordering the Mediterranean Sea, including Pakistan, India, and Iran [26]. It is traditionally used for the treatment of bronchitis, asthma, cough, diarrhea, rheumatism, influenza, and skin disorders[27]. The black seed contains fatty acids such as linolic acid, oleic acid, dihomolinoleic acid, eicodadienoic acid, palmitic acid, stearic acid, thymoquinone, thymohydroquinone, dithymoquinone, *p*-cymene, carvacrol, α-pinene, thymol, quercetin, kaempferol, quercetin-3as well as proteins, alkaloids, saponins, vitamins, minerals, and carbohydrates[27, 28].

These components have antioxidant, anti-inflammatory, immunomodulatory, anticancer, neuroprotective, antimicrobial, antihypertensive, cardioprotective, antidiabetic, gastroprotective, nephroprotective, and hepatoprotective properties[29]. Studies have reported black seed's protective effect against paracetamol through decreasing anti-inflammatory, increasing antioxidant, and GSH levels [27, 30]. The animal dosage of black seed extract used in studies ranges from 500-1000 mg/kg/day [27, 30] and 0.3-2 ml/kg/day of black seed oil [26, 28].

Cardamom (*Elettaria cardamomum*)

Cardamom, the queen of spices, is a sweet, aromatic flavor that belongs to the Zingiberaceae family [31]. Cardamom is a perennial herbaceous plant that contains phenols, starch, tannins, terpenoids, flavonoids, proteins, sterols, anthocyanins, and alkaloids [32]. Cardamom's therapeutic benefits stem from its pharmacological characteristics, which include anti-oxidant, antimutagenic, antibacterial, anti-inflammatory, anti-diabetic, cardioprotective, hepatoprotective, and chemoprotective properties [33]. Studies reported that cardamom can attenuate paracetamol toxicity by inhibiting ROS production and upregulating the Nrf2/HO-1/NQO-1 pathway with subsequent mitigation of oxidative stress, inflammation, and apoptosis [31, 34]. The dosage of cardamom used in studies was 200mg/kg/day for cardamom aqueous extract [31] and 100mg/kg/day for cardamom oil [34].

Coffee (*Coffea arabica (arabica)/Coffea cabephora (robusta)*

Coffee is a member of the Rubiaceae family, and the genus Coffea is typically grown in subtropical and tropical climates, with 90 to 124 species [35]. Coffee is one of the most consumed beverages worldwide and is popular for its characteristic flavor and rich organoleptic properties [36]. Coffee contains protein, carbohydrates, lipids, and minerals in addition to other bioactive components including caffeine,

nicotinic acid, chlorogenic acids, diterpenes, trigonelline formic acid, and acetic acid [37].

These compounds have beneficial effects on human health, including high antioxidant, anti-inflammatory, antimutagenic, and antidiabetic activity, and hepatoprotective cardiovascular protective activity [36]. Studies reported that coffee can attenuate paracetamol toxicity by downregulating lipid peroxidation, and CYP2E1 gene expression, and increasing GSH [38, 39]. The dosage of coffee used in studies on humans ranges from 1-3g/kg/day.

Costus or Qist Hindi *(Saussurea lappa)*

Costus is a medicinal plant in the Asteraceae family that has been referenced in the Holy Ahadith said by Prophet Muhammad (Peace be upon him) for the treatment of many diseases [40]. Costus has been found to have antifungal, anthelmintic, antidiabetic, antitumor, antimicrobial, immunostimulant, antiulcer, anti-inflammatory, and antihepatotoxic properties [41]. Antifungal, anthelmintic, antidiabetic, antitumor, antimicrobial, immunostimulant, antiulcer, anti-inflammatory, and antihepatotoxic characteristics have been discovered for costus [40]. Antioxidants found in the costus may combat germs, fungi, worms, cancers, inflammation, ulcers, diabetes, and liver damage while also boosting the immune system [42]. Costus can be used as an elective antioxidant operator in both the medical and food industries by scavenging nitric oxide (NO), 2,2-diphenyl-1-picrylhydrazyl, and superoxide radicals with lipid peroxidation inhibition. The anti-inflammatory action of costus may be related to the maintenance of lysosomal membranes with an antiproliferative consequence as well as inhibiting tumor necrosis factor-alpha (TNF-α) and NO and proliferated lymphocytes $CD4^+$ and $CD8^+$ via conjugation with sulfhydryl groups of target proteins [43]. The extract of costus was given to rabbits at a dose of 300 mg/kg/day to prevent paracetamol toxicity [41].

Curcumin or Turmeric (*Curcuma longa*)

Turmeric is an herbaceous and aromatic plant that belongs to the Zingiberaceae family[44]. Curcumin is a polyphenol found in the yellow flowers of turmeric grown in China and India [12]. Traditionally, curcumin has been used for liver disorders [13]. Curcumin has hepatoprotective, nephroprotective, antioxidant, anti-inflammatory, antitumor, antidiabetic, wound healing, anti-allergic, anti-dementia, and free radical scavenger properties [12, 45]. In addition, curcumin is believed to be a powerful agent against diseases such as anorexia, diabetes, liver diseases, rheumatism, Alzheimer's, bile-related disorders, and sinusitis [12].

Curcumin has been found to have hepatoprotective effects against paracetamol-induced liver damage through its antioxidant and anti-inflammatory properties [45]. Studies reported that curcumin can diminish paracetamol-induced liver injury by activating antioxidant activity and reducing pro-inflammatory cytokine production thus reversing mitochondrial dysfunction caused by NAPQI [4, 46, 47]. The animal dosage of curcumin used in studies ranges from 100-200 mg/kg/day.

Dandelion (*Taraxacum officinale*)

Taraxacum officinale is an edible plant in the Asteraceae family[48]. Dandelion is a plant that is widely distributed in the northern hemisphere and is traditionally used as a laxative, choleretic, diuretic, antirheumatic, and anti-inflammatory remedy [8, 10]. Dandelion contains many antioxidants, and anti-inflammatory and antimicrobial agents including terpenes, phenolic acids, flavonoids, alkaloids, peptides, oligosaccharides, polysaccharides, calcium, potassium, vitamins A, C, and nicotinic acid, with therapeutic effects on obesity, cancer, heart disease, diabetes, and gastrointestinal disorders [8, 10, 49]. Studies have shown that dandelion extract can reduce the severity of paracetamol-induced liver damage by boosting antioxidant activity, inhibiting lipid peroxidation, activating the Nrf-2/HO-1 pathway, and inhibiting the apoptosis pathway [8, 10, 49, 50]. The animal dosage used in these studies ranges from 100-400 mg/kg/day.

Date palm (*Phoenix dactylifera*):

The date palm is a tropical tree of the Arecaceae family[51]. It has been used in traditional medicine to

treat various ailments such as reparatory disorders, abdominal troubles, and liver injury [16]. Dates are a rich source of various nutrients such as dietary fibers, carbohydrates, proteins, lipids, vitamins, minerals, and biologically active components such as tannins, polyphenols, flavonoids, and carotenoids that possess antioxidant, anti-inflammatory, antimicrobial, antiallergic, antiatherogenic, anticancer, immunostimulatory, hepatoprotective, nephroprotective, and neuroprotective, properties [16, 52].

Studies have shown that both palm date extract and date seed extract can prevent paracetamol toxicity through increased antioxidant capacity, prevention of membrane lipid peroxidation, and suppression of CYP formation thus inhibiting NAPQI formation [5, 16, 52]. The animal dosage used in studies ranges from 50 to 400 mg/kg/day for palm date extract and 200 to 400 mg/kg/day for date seed extract.

Green tea (*Camellia sinensis*)

Camellia is the largest genus in the Theaceae family, and it is found in China and neighboring countries [53]. Tea has a long history of use in folk Asian medication for treating various health conditions such as inflammation, diabetes, digestive system disorders, heart conditions, and neurodegenerative diseases [54, 55]. Green tea is a popular beverage that contains polyphenols, catechins (epigallocatechin-3- gallate, epigallocatechin, epicatechin-3-gallate, and epicatechin), caffeine, minerals, and trace amounts of vitamins, amino acids, and carbohydrates [55, 56]. In addition to enhancing liver and kidney functioning, green tea components contain antioxidant, anti-inflammatory, antibacterial, antiviral, anti-diabetic, and anti-obesity properties [56, 57]. Studies have shown that green tea can reduce the severity of paracetamol-induced liver damage by affecting paracetamol metabolizing enzymes, increasing antioxidant capacity, and decreasing lipid peroxidation [56, 58]. The animal dosage used in studies ranges from 8.5- 200 mg/kg/day.

Ginger (*Zingiber officinale*)

Ginger is a member of the Zingiberaceae plant family, which contains 1300 species and 49 genera, including 80-90 Zingiber species[59]. Ginger is a tropical and sub-tropical plant, and it has been used traditionally for the treatment of rheumatism, gingivitis, toothache, asthma, stroke, nausea, vomiting, and diabetes [60]. The main constituents in ginger are carbohydrates, lipids, terpenes (zingiberene, β-bisabolene, α-farnesene, β-sesquiphellandrene, and α-curcumene), and phenols (gingerols, shogaols, and paradols) [61]. Ginger possesses multiple biological activities, including antioxidant, anti-inflammatory, antimicrobial, antidiabetic, anticancer, neuroprotective, cardiovascular protective, and respiratory protective activities [62]. Studies have shown that ginger can reduce the severity of paracetamol-induced liver damage through scavenging for free radicals and reducing lipid peroxidation, nitric oxide, and pro-inflammatory cytokines (TNF-α) [63-65]. The animal dosage used in studies ranges from 120- 600 mg/kg/day.

Longevity Spinach (*Gynura procumbens)*

Gynura procumbens is an Asteraceae family medicinal shrub [66]. Numerous studies have revealed that different extracts of *Gynura procumbens* leave contain a variety of active chemical constituents such as flavonoids, saponins, tannins, terpenoids, sterol glycosides, rutin, kaempferol, and two potential antioxidant components known as kaempferol-3-O-rutinoside and astragalin [67]. The flavonoid content of *Gynura procumbens* leaves has been shown to actively inhibit free radicals produced by peroxidation cytotoxicity and inhibit lipid peroxidation, and they serve as a binder of superoxide anions and hydroxyl radicals at the initiation stage [68]. Studies reported that *Gynura procumbens* extract has powerful antioxidant activity against paracetamol toxicity [66, 68]. The animal dosage of *Gynura procumbens* extract used in studies ranges from 100 to 300 mg/kg/day.

Jojoba (*Simmondsia chinensis*)

Jojoba is a member of the Simmondsiaceae family of perennial plants [69]. Jojoba a dioecious plant growing in desert and semi-desert areas such as Argentina, Chile, India, Tunisia, the Palestinian territories, and Egypt, has been used traditionally as a remedy for cancer, obesity, and throat warts [17, 70]. Its extracts contain flavonoid, gadolic acid, eicosanoic, docosenoic, oleic, linoleic, linolenic acids, palmitic, pentadecanoic, myristic, lauric acids, tocopherol, jojobenoic acid, and Jojobyl alcohols [70, 71]. Jojoba extract has antioxidant, Anti-fungal, anti-microbial, and anti-cancer properties [72]. A previous study showed that 0.6mg/kg/day jojoba extract can reduce the severity of paracetamol-induced by increasing the production of antioxidant enzymes, decreasing the production of oxidative biomarkers inside the liver, and inhibiting inflammatory proteins (TNF-α) [17].

Lemongrass (*Cymbopogon citratus*)

Lemongrass is an aromatic plant belonging to the Gramineae family that has been used in Asia, Africa, the Middle East, and Southeast cuisines [73, 74]. It contains polyphenols, flavonoids, steroids, lignins, alkaloids, terpenoids, carotenoids, vitamins, sesquiterpenes, lactones, and saponins [73, 75]. Those active ingredients have anions scavengers' activity, antioxidants, anti-inflammatory, antimicrobial capabilities, anti-mutagenicity, hypoglycemic and hypolipidemic properties [9, 73]. Studies suggest that treatment with lemongrass extracts reduces lipid peroxidation, and free radicals formation, and increases the generation of GSH thereby, ameliorating the liver and kidney injuries induced by paracetamol [9, 73, 76]. The animal's dosage of lemongrass extract used in studies ranges from 100-1000 mg/kg /day.

Licorice (*Glycyrrhiza glabra*)

Licorice is a member of the Fabaceae family [77]. It has been widely used as a medicinal herb in Chinese traditional therapy for treating digestive, immune, and cardiovascular system disorders [78]. The main chemical components in licorice are triterpenoid saponins, flavonoids, polysaccharides, coumarins, alkaloids, volatile oils, amino acids, and trace elements[78]. Glycyrrhizin an aqueous extract of licorice root is composed of glycyrrhetinic acid and two molecules of glucuronic acid [14]. The pharmacological effects of licorice extracts include adrenocortical hormone-like effects, and anti-inflammatory, antibacterial, antiviral, and antitumor effects [78].

Studies have shown that licorice extract can reduce the severity of paracetamol-induced liver damage in animals by increasing the production of glutathione peroxidase, stabilizing cellular membranes, attenuating the hepatic mitochondrial damage, and inhibiting the up-regulation of nNOS and enhancement of antioxidant enzymes [11, 14, 79]. The animal dosage of licorice extract used in studies ranges from 40- 200 mg/kg/day.

Milk thistle (*Silybum marianum*)

Milk thistle is an annual or biennial medicinal plant of the Asteraceae family [80]. Milk thistle is a traditional herbal remedy that has been used for liver problems for centuries [81]. The active compound in milk thistle, is silymarin, a polyphenolic component isolated from the fruits and seeds of the milk thistle plant [82]. Silymarin is a complex mixture of flavonolignans (silibinin, silychristin, silydianin, isosilybin, isosilychristin), flavonoids (taxifolin, quercetin), polyphenolic molecules, and fatty acids [81, 83, 84]. It has antioxidant and anti-inflammatory effects that protect liver cells from damage [81].

Silymarin is a traditional antioxidant herb used to treat liver disorders; as it scavenges free radicals and regulates the metabolism of the GSH pool [4]. A study has shown that administration of 100 to 600 mg/kg/day milk thistle can reduce the severity of paracetamol-induced liver damage in animals, by scavenging superoxide and attenuating ROS formation in the mitochondria, which results in reduced peroxynitrite formation [82].

Miswak or toothbrush (*Salvadora persica*)

Miswak belongs to the family Salvadoraceae, which was considered a medicinal herbal plant as long ago as 3000 years ago [85]. It contains chlorides,

salvadourea, salvadorine, alkaloids, fluoride, silica, sulfur, vitamin C, resin, tannins, saponins, flavonoids, cyanogenic glycosides, and benzyl isothiocyanate which show several pharmacological properties, including antibacterial and antifungal activities, anti-inflammatory and sedative properties, antioxidants, anti-plaque formations, anti hyperlipidemia and hypoglycemic [86]. A previous study showed that treatment with 500mg/kg/day of miswak extract alleviates paracetamol-induced hepatotoxicity, nephrotoxicity, and hematological toxicity through its antioxidant and anti-inflammatory activity [87].

Pomegranate (*Punica granatum*)

Pomegranate is a Lythraceae fruit-bearing delicious shrub. Pomegranate juice and shell have marked antioxidant capacities. Pomegranate juice is composed of water, sugar, pectin, ascorbic acid, polyphenols (anthocyanins and ellagitannins), polyphenolic acids (elaic and galic acid), and flavonoids (quercetin, kaemferol, and luteolin glycosides) [88]. Pomegranate has antioxidant, anticancer, antidiabetic, neuroprotective, and cardioprotective effects [89]. A study reported that the administration of 1.5ml of pomegranate juice protected the liver against paracetamol toxicity through its powerful antioxidant capacity [88].

Rosemary (*Salvia rosmarinus)*

Rosemary (*Salvia rosmarinus)* formally called *Romarinus Officinalis* **is a** Mediterranean plant [90]. It is a tiny evergreen shrub in the Lamiaceae family [91]. It contains carnosol, carnosic acid, ursolic acid, rosmarinic acid, caffeic acid, flavonoids, polyphenols, terpenoids, and volatile oils [92, 93]. Rosemary has various health-promoting properties, including hepatoprotective, therapeutic potential for Alzheimer's, and gastrointestinal disorders, and anti-cancer properties due to its richness in phytochemicals with antioxidant, anti-inflammatory, antimicrobial, and antimutagenic properties [90, 92]. A study has shown that the administration of 125mg/kg/day rosemary can prevent paracetamol toxicity by scavenging ROS, inhibiting lipid peroxidation, and upregulating the antioxidant defense [90].

Roselle (*Hibiscus sabdariffa Linn*)

Hibiscus sabdariffa Linn is an annual plant in the Malvaceae family that has been found to contain phenolic compounds, anthocyanins, flavonols, and protocatechuic acid [94]. The plant's calyces have been found to contain important nutrients such as protein, fat, carbohydrates, fiber, vitamin C, beta-carotene, calcium, and antioxidants such as anthocyanin, quercetin, and protocatechuic acid [95]. Roselle extract's antioxidant activity is due to its strong scavenging impact on reactive oxygen and free radicals [96]. The dosage of an ethanolic aqueous extract of *Hibiscus sabdariffa* Linn calyx against paracetamol toxicity varies between 200 and 250 mg/kg/day [94, 97].

Seablite (*Suaeda vermiculata Forssk)*

Suaeda vermiculata Forssk, a plant in the Amaranthaceae family, grows in central Saudi Arabia and other Mediterranean areas [98]. It contains a high concentration of phenolics and flavonoids, which have strong protective properties, as well as hypoglycemic, hypolipidemic, and antitumor properties [99]. A study reported that 400mg/kg/day of *Suaeda vermiculata* extract can reduce paracetamol toxicity by increasing the antioxidant enzyme activities of superoxide dismutase and catalase [98].

Sumac (*Rhus coriaria*)

Sumac belongs to the Anacardiaceae family's Rhus genus and has roughly 250 species [100]. Sumac fruits are commonly used as a beverage, spice, or natural source of edible oil [15]. Sumac is traditionally used to treat cancer, stroke, diarrhea, hypertension, dysentery, haematemesis, ophthalmia, stomach ache, diuresis, diabetes, atherosclerosis, measles, smallpox, liver disease, teeth and gum ailments, headaches, animal bites, dermatitis, and liver disease[101]. its potential therapeutic effect has been evaluated by several studies that identified its antibacterial, antifungal, antioxidant, antilipidemic, hypoglycemic, and hepatoprotective properties [101, 102]. Sumac contains a variety of medicinally active components,

including organic acids, phenolic acids, flavonoids, anthocyanins, hydrolyzable tannins, terpenoids, proteins, fiber, volatile oils, fatty acids, vitamins, and minerals [101, 102].

Studies reported that sumac can attenuate paracetamol toxicity by increasing antioxidant capacity, inhibiting lipid peroxidation, and reducing pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β) secretion [15, 103, 104]. The animal dosage of sumac used in studies ranges from 50-5000mg/kg/day.

Sunflower (*Helianthus annuus*)

Sunflower is one of the four most significant annual crops in the world for edible oil, and it is a member of the Compositae family [105]. The sunflower plant includes a variety of chemicals, including alkaloids and phenolics in the leaves, saponin in the flower parts, a polyphenol in the root part having alkaloids, and fatty acids and tannins in the seeds, which make it useful as an antimalarial, antiasthmatic, antioxidant, and antimicrobial agent [106]. Sunflower methanol extract has been reported to have effective radical scavenging properties as well as potential hepatoprotective activity, which could be attributed in part to its antioxidant activity and high phenolic content [107]. The dose of sunflower methanolic extract used to treat paracetamol toxicity varied from 100 to 500 mg/kg/day [107].

Sweet orange fruit (*Citrus sinensis*)

Orange fruit belongs to the Rutaceae family, it contains soluble sugars, starch, cellulose and hemicellulose fibers, lignin, and pectin [108]. Oranges also contain alkaloid, flavonoid, tannin, saponin, and steroid components that can scavenge nitric oxide and prevent lipid peroxidation, giving them many health benefits such as anti-cancer, anti-microbial, antioxidant, anti-ulcer, anti-inflammatory, hypolipidemic, and hepatoprotective properties [109]. Studies have shown that oranges can protect against paracetamol toxicity due to their strong antioxidant capacity which aids in preventing the peroxidation of membranous polyunsaturated lipids thus helping in the maintenance of membrane integrity, increasing GSH and reducing the levels of hepatic enzymes [108, 110]. The animal dosage of sweet oranges used in studies ranges from 125 to 600mg/kg/day.

Limitations and challenges of natural products

Despite their potential therapeutic benefits, natural products also have limitations and challenges that need to be considered. Natural products with protective activity against paracetamol along with their mechanisms of action are collected in Table 1. One major challenge is the lack of standardization and quality control, as natural products can vary in composition and potency depending on the source, extraction method, and processing conditions. This can lead to inconsistencies in efficacy and safety, as well as potential drug interactions with other medications.

Another challenge is the limited understanding of the pharmacokinetics and pharmacodynamics of natural products, which can affect their absorption, distribution, metabolism, and elimination in the body. This can lead to unpredictable outcomes and potential toxicity if the dose and duration of natural product use are not properly monitored and controlled.

Future directions and conclusions

Despite the challenges and limitations, natural products have shown promise as potential therapeutic agents for paracetamol toxicity. Further research is needed to elucidate their mechanisms of action, optimize their dosing and formulation, and evaluate their safety and efficacy in clinical trials.

In conclusion, paracetamol toxicity is a serious medical condition that can lead to acute liver failure and death if left untreated. Natural products, including phytochemicals and herbal extracts, have shown potential as protective agents against paracetamol toxicity by mitigating oxidative stress, inflammation, and cellular damage. Many natural plants have been shown to possess the ability to ameliorate paracetamol toxicity; these are mentioned in Figure. 2. However, further research is needed to fully understand their therapeutic potential and limitations, as well as to address issues related to standardization, quality control, and drug interactions.

Table 1: Natural products with protective activity against paracetamol toxicity

Scientific name	Family	Mechanism	Dosage	References
Aloe vera (*Aloe barbadensis*)	Liliaceae	Increase antioxidants	400 -500 mg/kg/day	(2, 3)
Basil or Rehan (*Ocimum basilicum*)	Lamiaceae	Increase antioxidants and free radical scavenging	200- 400 mg/kg/day	(20-22)
Black mulberry (*Morus nigra*)	Moraceae	Increase antioxidants and stimulated GSH formation	150 to 500 mg/kg/day	(1, 24)
Black seed (*Nigella sativa*)	Ranunculaceae	Increase antioxidants, decrease lipid peroxidation, and stimulated GSH formation	500-1000mg/kg/day	(27, 30)
Cardamom (*Elettaria cardamomum*)	Zingiberaceae	Increase antioxidants, inhibit ROS formation, and stimulate Nrf2/HO-1/NQO-1 pathway	200mg/kg/day	(31, 34)
Coffee (*Coffea arabica* (arabica)/ Coffea *cabephora (robusta)*	Rubiaceae	Downregulate CYP2E1 gene expression, and increase GSH	1-3g/kg/day	(38, 39).
Costus or Qist Hindi (*Saussurea lappa*)	Asteraceae	Increase antioxidants and decrease inflammation	300 mg/kg/day	(43)
Curcumin or Turmeric (*Curcuma longa*)	Zingiberaceae	Increase antioxidants, and decrease inflammation and NAPQI formation	100-200 mg/kg/day	(4, 46, 47)

Dandelion (*Taraxacum officinale*)	Asteraceae	Increase antioxidants and activation of the Nrf-2/HO-1 pathway	100-400 mg/kg/day	(8, 10, 49, 50).
Date palm (*Phoenix dactylifera*)	Arecaceae	Increase antioxidants, and prevent the formation of CYP and NAPQI	200 to 400 mg/kg/day	(5, 16, 52).
Ginger (*Zingiber officinale*)	Zingiberaceae	Increase antioxidants, free radical scavenging, and prevent the formation of NO and TNF-α.	120- 600 mg/kg/day	(63-65)
Green tea (*Camellia sinensis*)	Theaceae	Increase antioxidants and suppress CYP formation	8.5- 200 mg/kg/day	(56, 58)
Longevity Spinach (*Gynura procumbens)*	Asteraceae	Increase antioxidants	100- 300 mg/kg/day	(66, 68)
Jojoba (*Simmondsia chinensis*)	Simmondsiaceae	Increase antioxidants, and decrease inflammatory cytokines and TNF-α	0.6mg/kg/day	(17)
Lemongrass (*Cymbopogon citratus*)	Gramineae	Increase antioxidants, free radical scavenging, and GSH formation	100- 1000 mg/kg /day	(9, 73, 76)
Licorice (*Glycyrrhiza glabra*)	Fabaceae	Increase antioxidants, GSH and inhibit NOS	40- 200 mg/kg/day	(11, 14, 79)
Milk thistle (*Silybum marianum*)	Asteraceae	Increase antioxidants, free radical scavenging, and decrease ROS formation	100 to 600 mg per day	(82)

Miswak (*Salvadora persica*)	Salvadoraceae	Increase antioxidants, and decrease inflammatory responses	500mg/kg/day	(87)
Pomegranate (*Punica granatum*)	lythraceae	Increase antioxidants	1.5ml/kg/day	(88)
Roselle (*Hibiscus sabdariffa Linn*)	Malvaceae	Increase antioxidants, and free radical scavenger	200- 250 mg/kg/day	(94, 97)
Rosemary (*Salvia rosmarinus*)	Lamiaceae	Increase antioxidants, free radical scavenging, and inhibit lipid peroxidation	125mg/kg/day	(90)
Seablite (***Suaeda vermiculata)***	Amaranthaceae	Increase antioxidants	400mg/kg /day	(98)
Sumac (*Rhus coriaria*)	Anacardiaceae	Increase antioxidants, inhibit lipid peroxidation, and pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β) formation	50-5000 mg/kg/day	(15, 103, 104)
Sunflower (*Helianthus annuus*)	Compositae	Increase antioxidants	100-500 mg/kg/day	(107)
Sweet orange fruit (*Citrus sinensis*)	Rutaceae	Decrease lipid peroxidation and increase GSH formation	125- 250mg/kg /day	(108, 110)

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